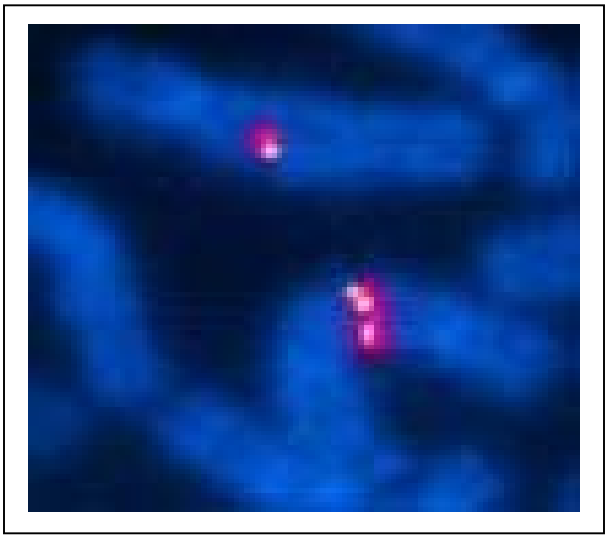
UPDATE: Laboratory of Neurogenetics

National Institute on Aging | *October 2003* | National Institute of Neurological Disorders & Stroke

Triplication of Synuclein Gene Found to Cause Form of Familial Parkinson Disease

In June of 2003, Dr. Andrew Singleton, of the Laboratory of Neurogenetics at the National Institute of Aging, found a small abnormality in chromosome 4 in people with Parkinson's disease in a large Iowan kindred. His findings represent a breakthrough in what had been an 80+ year research endeavor originating at the Mayo Clinic and continuing at NIH.



The picture shows both copies of chromosome 4 from a member of the family with Parkinson's disease. The dots on each chromosome show the loci for the gene making the protein called "synuclein". Normally, each person (in the world) has one copy of the synuclein gene on one of their chromosome 4, and another on the other chromosome 4. The top chromosome pictured contains only one white and pink dot. This is normal. Chromosome 4 appearing in the bottom right quadrant of the picture contains the abnormality. It shows 3 dots, representing three copies of the synuclein gene. Three copies mean that three times as much synuclein is made compared to normal. Individuals with this version of chromosome 4 will therefore make too much synuclein which builds up in their brain, ultimately leading to Parkinson's disease.

In a general sense, this discovery gives researchers a real clue into the causes of some forms of familial Parkinson's disease. It will undoubtedly contribute to the ability of scientists to move closer to a cure for PD not just for this family, but others as well. It is difficult to guess how far away treatment based on this type of finding is, but a reasonable guess would be 10 to 15 years.

Pooling of the Gene Pool

NINDS DNA and Cell Line Repository expected to counter the refusal of some researchers to share DNA

To support its mission of reducing the burden of neurological illnesses and to support outstanding investigators funded through its research programs, the National Institute of Neurological Disorders and Stroke (NINDS) has established a Human Genetics Resource Center: DNA and Cell Line Repository (http://locus.umdnj.edu/ninds). The NINDS Human Genetics Resource Center is a growing bank for human cells, DNA samples, clinical data and information sources to accelerate research on the genetics of nervous system disorders. Its mission is to provide genetics support for scientists investigating pathogenesis in the central and peripheral nervous networks and information support for patients, families, and advocates. Current diseases for which DNA is being collected include Parkinson's, Epilepsy, Stroke, and Motor Neuron Diseases, including ALS, Primary Lateral Sclerosis, and SMA.

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In This Issue

Compiled by: John Werner
Premedical Research Volunteer

DJ1 Gene Abnormality Found to Cause Parkinson's Disease

Scientists have just released news of a hereditary cause of Parkinson's disease (PD). Abnormalities in a gene called DJ-1 (PARK7) were found in patients with PD from two different families; one from a small village in the Netherlands, and another from a small village in Italy. These patients had the hallmark PD signs (stiffness, slowing, tremor) but the symptoms started earlier (average age of onset, 31 years) and progressed at a much slower rate (average duration, 18 years.)

Understanding these gene mutations and predicting the consequences of these structural problems gives scientists and doctors the ability to intervene with drug therapies. Before scientists can begin developing interventions or treatments, there are several questions to answer: 1) How many patients with PD have abnormalities in DJ-1 (i.e., is it a common or rare risk factor for PD)?, 2) How many different DJ-1 abnormalities are there?, 3) Do DJ-1 abnormalities cause additional/different symptoms than typical PD?, 4) How "potent" are the abnormalities (i.e., will everyone who inherits a DJ-1 abnormality get PD)?

The Young Onset PD community can help us learn more about DJ-1 and about the causes of PD by participating in our study at the NIH. If you are interested please contact Melissa Hanson 301-451-6093 or hansonm@mail.nih.gov.

A Day at Our Clinic

If you, or a member of your family has been diagnosed with Parkinson's disease, you are eligible to participate in our voluntary genetics research study. As part of your participation, you will have the opportunity to talk with a study doctor and/or a research coordinator about any specific concerns you might have. In addition to completing a series of questionnaires detailing your medical history (including ancestry), you will also be asked to answer a number of questions in interview format. Further, all potential risk and benefits of the study will be disclosed.

In some cases, a family tree in graphic form will be drawn to determine a genetic pattern in your family. At this point, should you wish to proceed, you will be asked to provide a blood sample of approximately 7 tablespoons. The sample will aid our team of research scientists in determining if you have a gene that may be related to your specific disorder. This will facilitate a better understanding of movement disorders and may eventually result in improved treatments or disease management.

See VISITING p. 3

GENE POOL, from p. 1

Centralization in the storage of genetic material not only decreases duplicative sampling efforts but gives participants the opportunity to make a maximal contribution to genetics research.

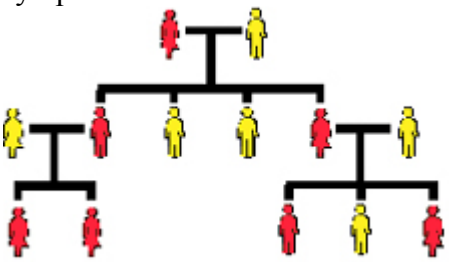
The NINDS repository allows receipt, storage, maintenance, standardization, quality control, and equitable, ethical distribution of DNA and other resources important to research in Neurological diseases. Moreover, the pooling of genes encourages work by junior investigators, researchers with novel approaches, and others not included in current collaborations, without excluding those who are established in their fields. Biomaterial samples held in the repository are only made available to investigators at recognized institutions who have adequate training and expertise to utilize the materials. Moreover, eligible investigators must agree to adhere to strict privacy protocol and conditions of use which include a prohibition against commercialization of products.

Venous blood is the primary sample sought, although other tissues of particular importance to neurological diseases may be included as they become available and as research opportunities demand.

Genetics 101, Our Approach to Genetic Studies Made simple

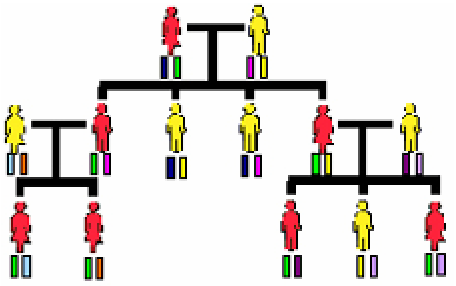
By Andrew Singleton, PhD

Take the family below for example; in this family there are a set of grandparents with four children. Two of these children also have children (2 girls in one instance, 2 boys and 1 girl in the other). Let us say the people shaded in red have Parkinson's disease, the ones in yellow have no symptoms.



The number of PD cases observed in this family is well in excess of what you would normally expect. When a situation like this occurs it generally means one of two things; there is a shared environmental factor that is causing the disease or there is a genetic predisposition to disease. The occurrence of PD in multiple generations in this family makes the second option the more likely.

The genome is comprised 22 pairs of chromosomes: 2 X chromosomes (female) or an X and a Y chromosome (male). Every cell in the body contains a copy of the genome. We inherit one half of each pair of chromosomes from our father and the other from our mother. In turn we then pass on a mixture of our fathers and mothers chromosomes to our children. Within these chromosomes are around 35,000 genes, which contain the instructions on how to produce proteins. Most often diseases such as the inherited PD seen in this pedigree are caused by a single change in a single gene. Currently it is impossible to look at all 35,000 genes at once, so, in order to find this change we have to narrow down the number of genes we need to examine. To do this we use a technique called linkage. Basically we examine small regions of the genome and follow the inheritance of that section through a family. Lets look at the family again, with additional genetic information.



Imagine the colored bars represent a small section of the genome (let's say about 1/1000th). Again it's important to remember that each section of the genome comes as a pair, half inherited from your father and half from your mother.

See 101 p. 4

VISITING, from p. 2

Blood samples will be obtained at NIH, by an associate in the field, or via a mailer kit which will allow you to have your blood drawn locally after which you can forward it to us by mail. Those wishing to come to NIH to have their blood drawn will have the added benefit of being able to receive a comprehensive evaluation by a Parkinson's disease specialist. In addition, you will be able to participate in our weekly clinical meeting where you case will be discussed among members of our prominent research team.

Should you opt to come to NIH, you will be asked to provide several dates on which you would be available to visit. We generally see patients on Mondays. Patients have the option of coming to the Washington DC area on either Sunday or Monday morning. They then depart on Monday evening or Tuesday depending on preference. NIH will cover all travel and lodging expenses for you and a companion.

We encourage you to solicit the participation of your family member(s) with PD. As our research is genetics based, it is greatly enhanced when we are able to track disease progression among multiple members of the same family.

101, from p. 3

Using "markers" we can distinguish between the two halves of these pairs and trace their inheritance through a family. This allows us to find a section of the genome that is always inherited with disease. Geneticists call this segregation and you can see that in this family the bright green section of the genome is always inherited with disease. This tells us that the gene defect is somewhere around this region of the genome. The larger the family is the more confident we can be of this result. Usually this stage will allow us to narrow down the number of genes we are interested in to 300 or so. We then systematically examine each gene for a change (called a mutation) that is likely to cause disease. Technological advances over the last 10 years has meant that the whole process from finding families to finding mutations is a lot quicker, however this approach still generally takes 5 to 15 years of research!

So given the incredible amount of time and effort needed to find these mutations why do we do it? These discoveries allow us and others to transfer those genes and mutations into cells and mice in order to make a model which helps the field to better understand disease processes. As more is understood about the disease progression we can then use these models to test therapies. It is only by appreciating how a disease begins and progresses that scientists can make informed attempts at halting or reversing disease progression.

To learn more about neurological disorders and the types of treatment and research being done, please visit the following sites:

Laboratory of Neurogenetics NIA
http://www.grc.nia.nih.gov/branches/lng/lngindex.htm

American Parkinson Disease Association
www.apdaparkinson.com

American Speech-Language-Hearing Association
www.asha.org

Michael J. Fox Foundation
www.michaeljfox.org

National Parkinson Foundation
www.parkinson.org

Parkinson Action Network
www.parkinsonsaction.org

We Move - Worldwide Education & Awareness for Movement Disorders
www.wemove.org

Amanda Singleton, Clinical Research Coordinator and Long Time Friend to Patients in Our Studies Moves On.

Dear participants and their families,

I am a little sad, but also excited to announce that I will be resigning as Research Coordinator for the Neurogenetics laboratory. Over the past 4+ years, I've learned a great deal working with the scientists and doctors. I've also learned a great deal from the patients, caregivers, support group leaders, and families of those with Parkinson's disease. I've seen some important scientific discoveries made, and also had the pleasure of getting to know several of you personally. I am finishing coursework for my public health degree at John's Hopkins, and will spend the next few months working on my graduation thesis in biostatistics. Also, many of you have heard about, seen, and in some cases had the chance to meet my 17-month-old daughter Emily, and I'm really looking forward to being at home with her. My husband Andy, whom many of you have met as well, will be sure to keep me up to date with the latest genetic findings in PD. I wish the best to all of you, and thank you for making my experience with the Laboratory of Neurogenetics very rewarding.

-Amanda